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P.D. 00-00-00

P. 1-5



1/5 - (C) FILE CAPLUS

STN CA Caesar accession number : 1911

AN - 2001:763989 CAPLUS

DN - 136:95580

TI - Photochemically enhanced binding of small molecules to the tumor necrosis factor receptor-1 inhibits the binding of TNF-.alpha.

IN - Carter, Percy H.; Scherle, Peggy A.; Muckelbauer, Jodi A.; Voss, Matthew E.; Liu, Rui-Qin; Thompson, Lorin A.; Tebben, Andrew J.; Solomon, Kimball A.; Lo, Yvonne C.; Li, Zhong; Strzemienski, Paul; Yang, Gengjie; Falahatpisheh, Nikoo; Xu, Meizhong; Wu, Zhongren; Farrow, Neil A.; Ramnarayan, Kal; Wang, Jing; Rideout, Darryl; Yalamoori, Venkatachalapathi; Domaille, Peter; Underwood, Dennis J.; Trzaskos, James M.; Friedman, Steven M.; Newton, Robert C.; Decicco, Carl P.

CS - Experimental Station, DuPont Pharmaceuticals Company, Wilmington, DE, 19880-0500, USA

SO - Proceedings of the National Academy of Sciences of the United States of America (2001), 98(21), 11879-11884  
CODEN: PNAS6; ISSN: 0027-8424

PD - National Academy of Sciences

DI - Journal

LA - English

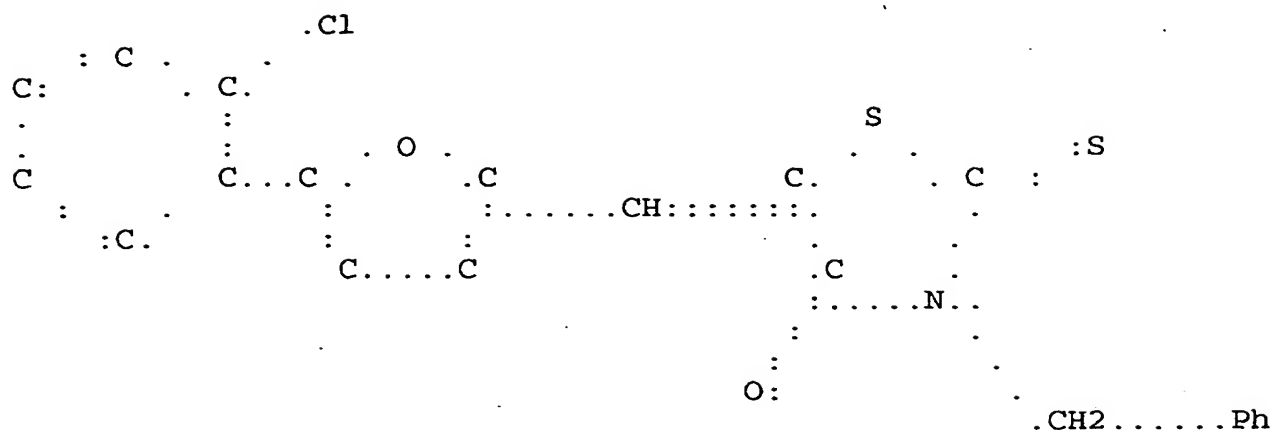
AB - The binding of tumor necrosis factor alpha (TNF-.alpha.) to the type-1 receptor (TNFRc1) plays an important role in inflammation. Despite the clin. success to biologics (antibodies, sol. receptors) for treating TNF-based autoimmune conditions, no potent small mol. antagonists have been developed. Our screening of chem. libraries revealed that N-alkyl 5-arylidene-2-thioxo-1,3-thiazolidin-4-ones were antagonists of this protein-protein interaction. After chem. optimization, we discovered IW927, which potently disrupted the binding of TNF-.alpha. to TNFRc1 (.apprx. 50 nM) and also blocked TNF-stimulated phosphorylation of I.kappa.-B in Ramos cells (IC50 = 600 nM). This compd. did not bind detectably to the related cytokine receptors TNFRc2 or CD40, and did not display any cytotoxicity at concns. as high as 100 .mu.M. Detailed evaluation of this and related mols. revealed that compds. in this class are "photochem. enhanced" inhibitors, in that they bind reversibly to TNFRc1 with weak affinity (.apprx. 40-100 .mu.M) and then covalently modify the receptor via a photochem. reaction. We obtained a crystal structure of IV703 (a close analog of IW927) bound to the TNFRc1. This structure clearly revealed that one of the arom. rings of the inhibitor was covalently linked to the receptor through the main-chain nitrogen of Ala-62, a residue that has already been implicated in the binding of TNF-.alpha. to the TNFRc1. When combined with the fact that our inhibitors are reversible binders in light-excluded conditions, the results of the crystallog. provide the basis for the rational design of nonphotoreactive inhibitors of the TNF-.alpha.-TNFRc1 interaction.

IT - 389122-24-1      389122-25-2      389122-26-3  
389122-27-4      389122-28-5      389122-29-6  
389122-30-9      389122-31-0      389122-32-1  
389122-33-2      389142-47-6 , IV 563

RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); P (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (photochem. enhanced binding of N-alkyl 5-arylidene-2-thioxo-1,3-thiazolidin-4-ones to tumor necrosis factor receptor-1 inhibits binding of TNF-.alpha.)

RN - 389122-24-1 CAPLUS

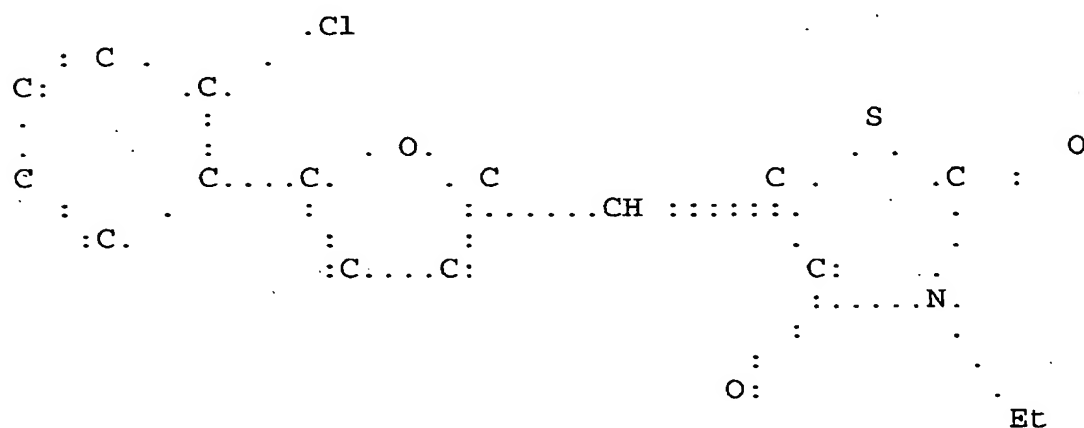
CN - 4-Thiazolidinone, 5-[[5-(2-chlorophenyl)-2-furanyl]methylene]-2-thioxo (5Z) - (9CI) (CA INDEX NAME)



STEREO DIAGRAM AVAILABLE WITH GRAPHICS TERMINAL OR OFFLINE PRINT

RN 389122-28-5 CAPLUS

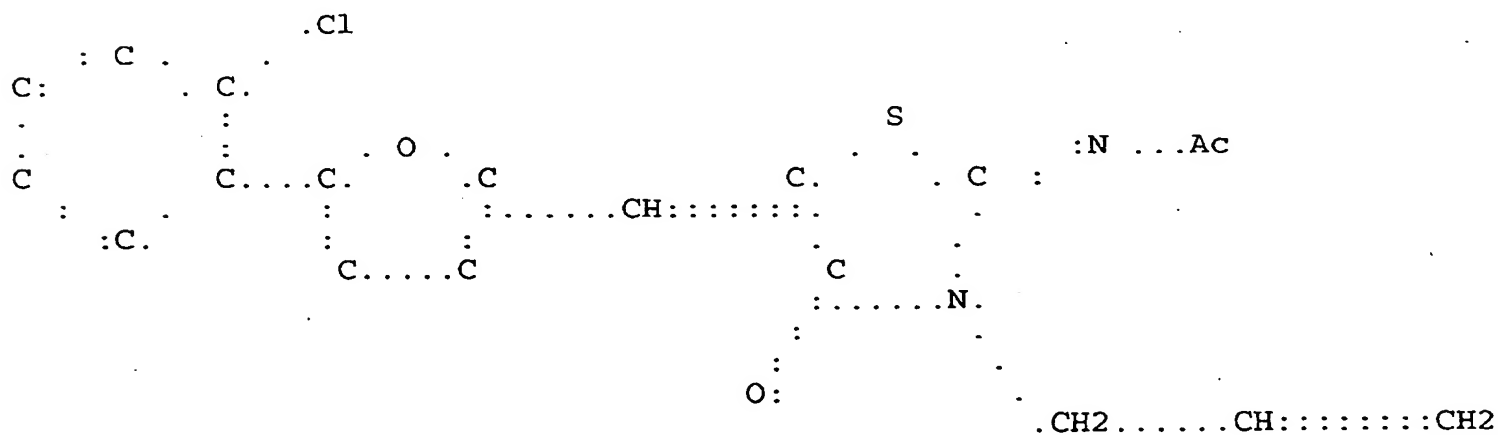
CI 2,4-Thiazolidinedione, 5-[[5-(2-chlorophenyl)-2-furanyl]methylene]-3-eth  
(5Z)- (9CI) (CA INDEX NAME)



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RN 389122-29-6 CAPLUS

CN Acetamide, N-[(5Z)-5-[[5-(2-chlorophenyl)-2-furanyl]methylene]-4-oxo-3-(propenyl)-2-thiazolidinylidene]- (9CI) (CA INDEX NAME)



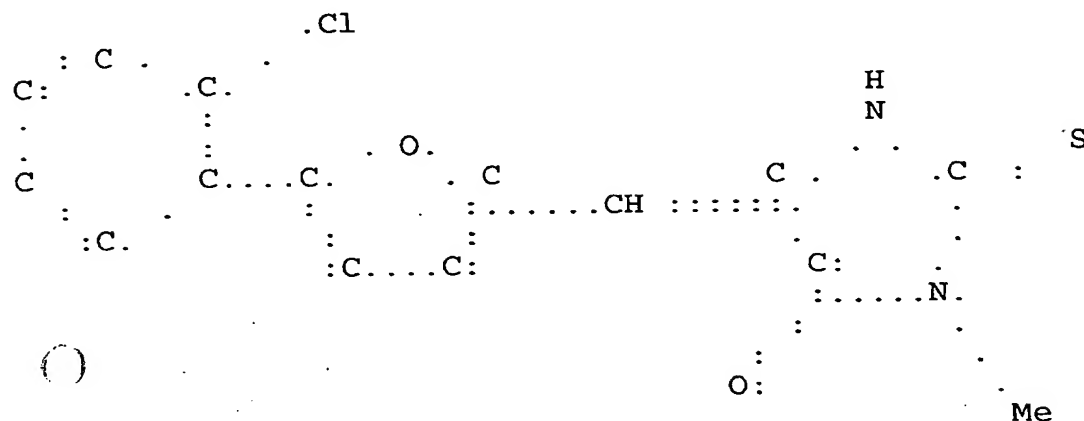
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RN 389122-33-2 CAPLUS

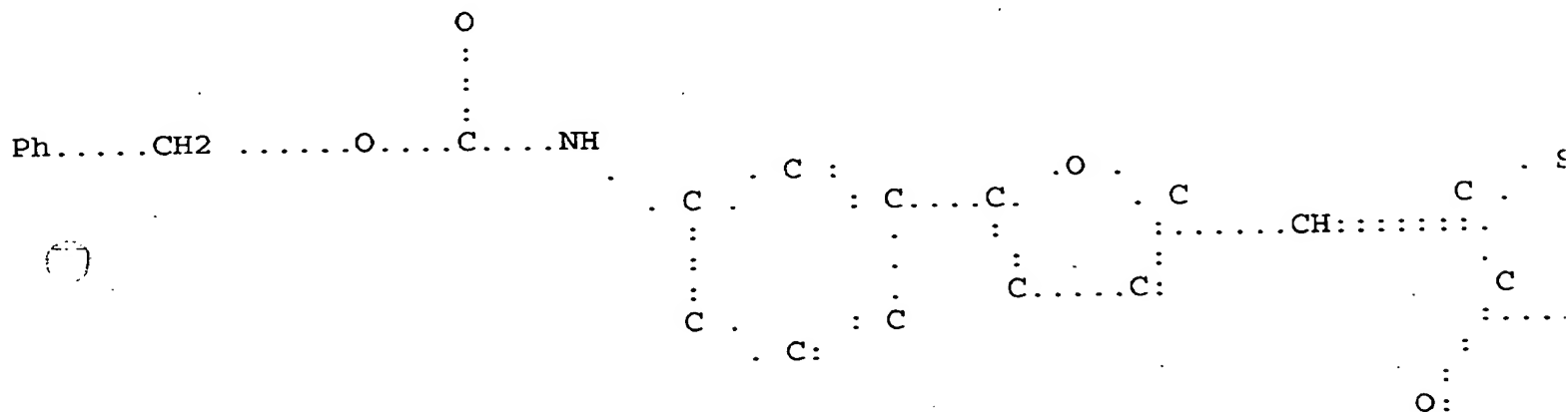
CN 4-Imidazolidinone, 5-[[5-(2-chlorophenyl)-2-furanyl]methylene]-3-methyl-  
thioxo-, (5Z)- (9CI) (CA INDEX NAME)



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RN 389142-47-6 CAPLUS

CN Carbamic acid, [3-[5-[(Z)-(3-ethyl-4-oxo-2-thioxo-5-thiazolidinylidene)methyl]-2-furanyl]phenyl]-, phenylmethyl ester (9CI)  
(CA INDEX NAME)



Page 1-A

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Page 1-B

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RE.CNT 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD